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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,520	09/01/2005	Masahiro Kajino	3125 US0P	5080

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
02/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,520	KAJINO ET AL.	
	Examiner	Art Unit	
	Kahsay T. Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-19* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19 are pending in this application.

Information Disclosure Statement

2. Applicant's Information Disclosure Statement, filed on 03/13/2006 has been acknowledged. Please refer to Applicant's copies of the 1449 submitted herewith.

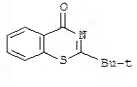
Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8-10 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Gade et al. *Chemische Berichte* (1992), 125(1), 127-141. Cited reference teaches the following compound of interest that is the same as applicant's compound when applicant's compound formula has the following substituents:

RN 137092-58-1 CAPLUS
CN 4H-1,3-Benzothiazin-4-one, 2-(1,1-dimethylethyl)- (CA INDEX NAME)



R^1 = H, n = 0, and R^2 = tert-butyl.

This compound is disclosed at page 131 (see compound 39) of said reference.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is recited in claim 18, "A method for preventing or treating cardiovascular diseases, bone or joint diseases, infectious diseases, inflammatory diseases or kidney diseases, but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the

art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claim 29 is are directed to a method for preventing or treating cardiovascular diseases, bone or joint diseases, infectious diseases, inflammatory diseases or kidney diseases which comprises administering an effective amount of the compound according to claim 1.

a. Scope of use - The scope of use that applicants intend to claim is very broad. There is no such agent, which can treat infectious diseases generally. Infectious diseases are extremely broad. Some infectious diseases are caused by bacteria (i.e. meningitis, whooping cough, tetanus, syphilis, etc.), some are caused by virus (i.e. HIV, common cold, measles, chicken pox, etc), some are caused by fungus (i.e. athletic foot, etc.), some are caused by protozoa (i.e. Amebiasis, Giardiasis, Lesihmaniasis, Beaver fever, Toxoplasmosis, Trichomoniasis, etc.). Not only that the viral diseases are different from bacterial and fungal diseases, but the viral diseases as listed above are also different one from the other. The nature of effect, origin, symptom, incubation, diagonsis, etc., is different one from the other. The same is true for the bacteria caused diseases and fungal caused diseases.

For example, HIV (human immunodeficiency virus) is a human T-cellleukemia/lymphoma virus of the subfamily Lentivirinae that is the causative agent of the disease AIDS. AIDS is an acquired immunodeficiency syndrome, an epidemic

retroviral disease due to infection with human immunodeficiency virus (HIV-1), transmissible via blood or semen, and characterized by an ineffective immune response; the disease follows a protracted and debilitating course and has a poor prognosis.

There has been recited a method of treating bone or joint diseases in general, but the specification is not enabled for such a scope. Mature bone consists of: an organic matrix (osteoid) composed mainly of type 1 collagen formed by osteoblasts; a mineral phase which contains the bulk of the body's reserve of calcium and phosphorus in crystalline form (hydroxyapatite) and deposited in close relation to the collagen fibers; bone cells; and a blood supply with sufficient levels of calcium and phosphate to mineralize the osteoid matrix. Bone turnover and remodeling occurs throughout life and involves the two coupled processes of bone formation by osteoblasts and bone resorption by osteoclasts and perhaps osteolytic osteocytes. The metabolic bone diseases may reflect disturbances in the organic matrix, the mineral phase, the cellular processes of remodeling, and the endocrine, nutritional, and other factors which regulate skeletal and mineral homeostasis. These disorders may be hereditary or acquired and usually affect the entire bony skeleton. The acquired metabolic bone diseases are the more common and include: osteoporosis, osteomalacia, the skeletal changes of hyperparathyroidism and chronic renal failure (renal osteodystrophy), and osteitis deformans (Paget's disease of bone).

Osteoporosis - defined as a decrease in bone density (mass per unit volume) of normally mineralized bone, resulting in thinning and increased porosity of the bone cortices and trabeculae. The bone that remains, although diminished in amount, is normally mineralized and lacks the wide osteoid seams which are typical of osteomalacia and other disorders of bone mineralization. Osteoporosis is also a broadly used clinical term for a generalized loss of bone density resulting in skeletal fragility, bone pain, and pathological fractures (of the spine, wrist, hip, and ribs), particularly in postmenopausal women and both sexes with increasing age.

Osteopenia ("too little" bone) is a descriptive term for a loss of bone density observed radiologically. Osteopenia may be local (as in disuse atrophy of an immobilized limb) or generalized. There are many causes of generalized osteopenia, among them: osteoporosis unrelated to other disease, endocrinopathies (hypercortisolism, hypogonadism, hyperparathyroidism, hyperthyroidism), deficiency states (rickets/osteomalacia, scurvy, malnutrition), neoplastic diseases (multiple myeloma, metastatic carcinoma, leukemia), chronic diseases (malabsorption syndromes, chronic renal failure), drugs (glucocorticoids, heparin, alcohol), and hereditary diseases (osteogenesis imperfecta, homocystinuria).

Primary osteoporosis, unrelated to other disease, is classified by age groups into postmenopausal, senile, idiopathic (premenopausal women and younger men), and juvenile forms. Postmenopausal osteoporosis is the most frequent form of osteoporosis and is the commonest metabolic bone disease. The term involutional osteoporosis encompasses osteoporosis occurring in postmenopausal women and in both sexes with

increasing age. Osteoporosis is an underlying factor in most of the hundreds of thousands of fractures seen annually in the U.S. in women over 45 years of age.

Rickets and Osteomalacia- diseases resulting from vitamin D deficiency are rickets in infants and growing children and osteomalacia in adult life. The bone changes in both conditions are characterized by inadequate mineralization, resulting in a deficient amount of the mineral phase of bone and an excess of unmineralized osteoid. The osteoid excess is caused by a failure of the process of mineralization to keep up with the new formation of osteoid during bone formation and remodeling. In rickets, which mainly affects children between the ages of 6-30 months, inadequate mineralization occurs not only in bone but also in epiphysial cartilage at sites of endochondral ossification, resulting in growth disturbances, skeletal deformities, and susceptibility to fractures. Presenting symptoms of osteomalacia ("softness of bone") include diffuse skeletal pain, bone tenderness, and muscular weakness.

Bone Changes in Hyperparathyroidism (Generalized Osteitis Fibrosa Cystica, Von Recklinghausen's Disease of Bone) - the skeletal changes in hyperparathyroidism are characterized by diffuse or focal resorptive loss and fibrous replacement of bone due to an excess of osteoclastic over osteoblastic activity and caused by an over-production of parathormone (PTH) in primary or secondary hyperparathyroidism.
Primary hyperparathyroidism is a metabolic disorder in which parathyroid cells, either neoplastic or hyperplastic and in the absence of any known stimulus, secrete excessive

amounts of PTH. Primary hyperparathyroidism is usually caused by a functioning adenoma of a single parathyroid gland, less commonly by diffuse hyperplasia of all four parathyroid glands, and rarely by primary parathyroid carcinoma or multiple parathyroid adenomas.

Secondary hyperparathyroidism is associated with many conditions that lead to hypocalcemia and most often occurs as a consequence of the hyperphosphatemia and hypocalcemia of chronic renal failure. The complex bone changes in chronic renal failure are called renal osteodystrophy and include osteomalacia, rickets ("renal rickets"), osteitis fibrosa and other bone changes of hyperparathyroidism.

Some non-parathyroid carcinomas (arising in lung, kidney,or elsewhere and without bony metastases) may produce a PTH-like hormone associated with a syndrome resembling hyperparathyroidism. This syndrome is called pseudohyperparathyroidism or ectopic hyperparathyroidism and may be reversed by removal of the functioning tumor.

Primary hyperparathyroidism most frequently occurs in adults, has a peak incidence between the third and fifth decades and a female to male ratio of two or three to one, and is rarely seen in children under 10 years of age. Primary hyperparathyroidism, in the absence of renal disease, is characterized biochemically by hypercalcemia, hypophosphatemia, hypercalciuria, elevated serum alkaline phosphatase activity (in the presence of bone disease), and increased levels of PTH measured by radioimmunoassays.

Renal Osteodystrophy - renal osteodystrophy (or uremic bone disease) is the term for a complex group of bone disorders that occur in patients with chronic renal failure (CRF). The bone disorders in renal osteodystrophy include: osteomalacia of adults and rickets of children (so-called "renal rickets"); osteitis fibrosa and other bone changes of secondary hyperparathyroidism; osteopenia; and osteosclerosis. Renal osteodystrophy occurs more often in children than in adults and particularly in the presence of congenital renal anomalies, such as renal hypoplasia and polycystic kidneys, that are associated with the development of slowly progressive renal insufficiency.

Paget's Disease of Bone (Osteitis Deformans) - Paget's disease of bone (osteitis deformans) is a localized, although sometimes multifocal, skeletal disorder of unknown cause and is characterized by abnormal bone remodeling brought about by waves of bone resorption and reformation. The skeletal involvement may be limited to a single bone (monostotic) or affect many bones (polyostotic), notably the pelvis, femur, tibia, spine, and skull. The affected bones may be weakened by resorption or enlarged by reparative, although defective, new-bone formation. In the final stage of the disease, dense bone is formed, but it is poorly organized and predisposed to fracture and deformity. Paget's disease, particularly in its milder form, is a common skeletal disorder of the later decades of life. Patients may present with pain, enlargement, or deformity of involved bones or with pathological fracture, auditory, cardiac, or other complications of the disease. The cause of Paget's disease is unknown, evidence of the very low skill in this art.

Since bone diseases are very diverse as shown above, it is impossible to treat all bone-diseases in general. Thus, an enablement rejection is proper.

There has been recited the treatment of kidney diseases in general, but kidney diseases vary in nature one from the other. As known the kidney has several essential roles:

1. Filter waste out of the blood; 2. Retaining protein, glucose, minerals, and water; 3. Maintain balance of electrolytes, sodium, potassium and phosphorus; 4. Calcium absorption; 5. Make hormones that produce red blood cells; 6. Produce renin, which regulates water retention and influences blood pressure. The disorders vary one from the other. For example, Kidney Stones that are defined as a hard mass of calcium and oxalate or phosphates that separate from the urine and build up on the inner surfaces of the kidney. There are also struvite stones caused be infection in the urinary tract. Much less common are the uric acid stone and the rare cystine stone. Renal tubular acidosis, Cystic kidney diseases, and metabolic disorders (i.e. hyperparathyroidism) are also suspected of causing stones. Kidney infection is another renal disorder. Infection in kidney that is also called Pyelonephritis, it usually is from bacteria that spread from the bladder Causes can include: Cystoscopes (to examine the bladder and urethra), Enlarged prostate, Surgery, Catheters, and Kidney stones. Kidney failure also called end stage renal disease or ESRD is also another renal disease when both of kidneys fail. Since the diseases are different one from the other, it is not possible to treat kidney diseases in general.

It is recited a method of treating cardiovascular disease in general, but the specification is not enabled for such a scope. Cardiovascular embraces a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris; the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias; ischaemic heart disease including congestive heart failure and myocardial infarction; stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCA); elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol; arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound --- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that million of combinations of compounds can be created from the definitions, owing especially to broad scope of R1, n and R2.

(2). Direction of Guidance: Applicants indicate that the inhibiting of myocardial apoptosis would be effective for the prevention and treatment of heart failure syndrome at page 3 of the specification. The amount of direction or guidance is minimal. There is

no guidance for the treatment or prevention of the diseases recited in claim 18. It is also noted that generic dosage is disclosed (0.001 to 0.02 mg/kg), regardless of the nature of the diseases.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these 1,3-Benzothiazine-4-one compounds or indeed are in use for the treatment or the prevention of the diseases recited in claim 18.

(4). Working Examples: The working examples are limited only to 10 compounds that are tested for inhibitory activity of cardiomyocyte apoptosis. The minimal effective concentration in micro molar for said compounds are disclosed at page 67, but there is no way to convert these data into useful meaning.

(5). Nature of the Invention and Predictability: The invention is directed to treating or preventing diseases recited in claim 18 by inhibiting the activity of cardiomyocyte apoptosis. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Note that cardiovascular diseases, bone diseases and infectious diseases are especially unpredictable due to their complex nature. Please see above that shows different types of cardiovascular diseases, bone diseases and infectious diseases.

(6). The Quantity of Experimentation Necessary: Immense, because so many cancerous cells are covered; see part (1).

(7). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat all the diseases recited in claim 18.

In regard to prevention, to this day the only means available is the treatment of patients suffering for example from bacterial infection, but not the prevention of healthy patients from getting the diseases recited in claim 18 in the first place. It is recommended that applicants delete claim 18 to overcome this rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because the phrase "may have substituents" or "having optionally substituents" is indefinite. In the absence of the

specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed. Applicants have to recite all the substituents as it was done for example in claim 13.

b. In claim 1or elsewhere in the claims, the term "acyl" is indefinite. What is covered and what is not? Note that acyl in claim 1 is not substituted, but in claim 3 it is recited specific examples of an acyl group with different types of substituents. It is recommended that applicants insert the detailed definition of acyl in claim 1.

c. In claim 1 or elsewhere in the claims, the phrase "optionally substituted amino" is indefinite. In the absence of the specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

d. In claim 1 or elsewhere in the claims, the phrase "R^2 represents (1) an optionally substituted branched alkyl" is indefinite. In the absence of the specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed. What is covered and what is not? Is the substituent -CH(CN)CO-Ph considered as optionally substituted branched alkyl? Applicant's specification does not disclose the complete list. It is recommended that applicants recite specific branched alkyl substituents to overcome this rejection.

Likewise, the same issue applies for the phrase "homocyclic group". Applicants have to recite specific rings to overcome this rejection.

e. Claim 8 starts as a compound claim, but ends up as a method claim. Note that the intended use "which is capable of binding to a macrophage migration inhibitory factor" has no patentable weight. If applicants intend a compound claim, then claim 8 is a duplicate of claim 1. If applicants intend a method claim, then claim 8 should be written in a method claim language.

Likewise, the same problem appears in claim 9. It is recommended that applicants delete claims 8-9 to overcome this rejection.

f. Claim 11 is rejected because the composition has no carrier. Note that the composition claims 12-17 are substantial duplicates of claim 11. Intended use has no patentable weight. A pill is a pill regardless of its intended use.

g. In claim 10, the term "prodrug" is indefinite. Determining whether a given derivative definitely is or is not a prodrug involves more than routine experimentation. If the derivative is active, open-ended experimentation may be involved to determine for sure whether the compound is a prodrug or whether it is active in its own right. It is recommended that applicants delete claim 10 and delete the term "prodrug" from the claims e.g. claim 18.

h. Claim 18 provides for the use of compound for preventing or treating diseases such as cardiovascular, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 18 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper

definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Objection

7. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay T. Habte whose telephone number is (571)-272-0667. The examiner can normally be reached on M-F (9.00- 5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

/Kahsay T. Habte/
Primary Examiner, Art Unit 1624

February 21, 2008